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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/439,293	CABOT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-15,17-19,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-15,17-19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *NCBI search*.

DETAILED ACTION

This Office action is in response to the communication filed 8-17-04.

Claims 1, 3-8, 10-15, 17-19, 21 and 22 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-17-04 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Applicant's arguments with respect to claims 1, 3-8, 10-15, 17, 19, 21 and 22 under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, have been considered but are moot in view of the new ground(s) of rejection set forth below. Applicants' arguments filed 8-17-04 are addressed below, following the new 112, first paragraph rejection, as they pertain to the instant rejection.

Applicant's arguments with respect to claims 1, 3-8, 10-15, 17, 19, 21 and 22 under 35 U.S.C. § 103(a) have been considered but are moot in view of the new

ground(s) of rejection set forth below. Applicants' arguments filed 8-17-04 are addressed below, following the new rejection, as they pertain to the instant rejection.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 10-15, 17, 19, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of reversing drug resistance and increasing apoptosis comprising the administration of antisense targeting any glucosylceramide synthase. The specification and claims do not describe elements essential to the broad genus comprising antisense targeting any glucosylceramide synthase (see accompanying NCBI sequence search reporting the various isoforms of nucleic acids encoding glucosylceramide synthase, including from various species). The broad genus comprising antisense targeting any glucosylceramide synthase is very broad. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Concise structural features that could distinguish structures with the genus from others is missing from the disclosure. The specification fails to teach or

adequately describe a representative number of species in the broad genus claimed. Thus, Applicants were not in possession of the broad genus comprising antisense targeting nucleic acids encoding any glucosylceramide synthase.

Claims1, 3-8, 10-15, 17, 19, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for AdrR cells *in vitro* comprising the introduction of antisense targeted to the sequence of human glycosylceramide synthase disclosed by Ichikawa et al (Proc. Natl. Acad. Sci. USA, 93: 4638-4643, 1996) (referenced on page 11 and figure 1 of the specification), does not reasonably provide enablement for a method of reversing drug resistance and inducing apoptosis in vivo comprising the introduction of any antisense targeting any glucosylceramide synthase gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to the compositions and methods of reversing drug resistance and inducing apoptosis in any cancer cell *in vivo* comprising the administration by any route of an antisense targeting any nucleic acid encoding glucosylceramide synthase and optionally further comprising administration of a chemosensitizer or chemotherapeutic agent.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due

to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50; see entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety,

especially at 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided adequate guidance in the specification toward a method of inhibiting glucosylceramide synthase expression in vivo comprising the administration of any antisense oligonucleotide. Nor have Applicants provided guidance toward a method of reversing drug resistance or inducing apoptosis in vivo comprising the administration of antisense to glucosylceramide synthase. The specification teaches the in vitro inhibition of expression of glucosylceramide synthase following administration of a full length antisense that specifically targets the nucleic acid sequence disclosed by Ichikawa et al (Proc. Natl. Acad. Sci. USA, 93: 4638-4643, 1996) (referenced on page 11 and figure 1 of the specification). The specification also teaches a decrease in drug resistance and induction of apoptosis in MCF-7-AdrR cells in vitro following administration of full length antisense that specifically targets the nucleic acid sequence disclosed by Ichikawa et al (Proc. Natl. Acad. Sci. USA, 93: 4638-4643, 1996) (referenced on page 11 and figure 1 of the specification). One skilled in the art would not accept on its face the examples given in the specification of the in vitro targeting and inhibition of glucosylceramide synthase.using this full length antisense as being correlative or representative of the successful inhibition of expression of glucosylceramide synthase, and accompanying decrease in drug resistance and increase in apoptosis in cancer cells in an organism. This is in view of the lack of guidance in the specification and known unpredictability associated with the successful targeting and delivery of antisense to target cells

harboring glycosylceramide synthase in an organism, and the known unpredictability associated with achieving efficacy of antisense inhibition in vivo, and further whereby decrease in drug resistance and increased apoptosis of cancer cells is achieved in an organism.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods of reversing drug resistance and inducing apoptosis in any cancer cell *in vivo* comprising the administration by any route of an antisense targeting any nucleic acid encoding glucosylceramide synthase and optionally further comprising administration of a chemosensitizer or chemotherapeutic agent. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring glucosylceramide synthase, whereby its inhibition is achieved and further whereby decreased drug resistance and increased apoptosis is obtained in any cancer cells in an organism. Since the specification fails to provide any particular guidance for inhibiting the expression of glucosylceramide synthase in an organism and further whereby decreased drug resistance and increased apoptosis are provided, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Applicant's arguments filed 8-17-04 have been fully considered but they are not persuasive. Applicants argue that the instant specification adequately provides guidance for reversing drug resistance and inducing apoptosis in cancer cells by introducing antisense to glucosylceramide synthase. Applicants also argue that the in

vitro/in vivo models should be accepted as correlating - absent evidence to the contrary. Applicants are correct that the specification teaches the inhibition of expression of the target glucosylceramide synthase gene, decrease in drug resistance and induction of apoptosis in vitro using antisense. But, contrary to Applicants' assertions, the in vitro inhibition of glucosylceramide synthase gene, decrease in drug resistance and induction of apoptosis are not necessarily correlative or representative of the ability to obtain expression inhibition of a target gene, with an accompanying decrease in drug resistance and induction of apoptosis in an organism. The references of Branch, Crooke, Peracchi, Chirila and Agrawal all address the limitations of antisense delivery in an organism, and that the results obtained in vitro are not correlative of the ability to achieve target gene inhibition in an organism (see above). In addition, the ability to achieve in vivo effects using antisense for one target gene is not necessarily predictive of the ability to do so using a different antisense for a different target gene. Because of such unpredictability, the in vivo success for a particular antisense must be tested empirically. For these reasons, the instant invention is rejected for lacking enablement over the scope claimed.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lavie et al and Ichikawa et al, the combination in view of Milner and McKay insofar as the claims are drawn to a method of reversing drug resistance in a cancer cell in vitro comprising the administration of an antisense specifically targeting the nucleic acid encoding glycosylceramide synthase previously taught by Ichikawa et al (Proc. Natl.

Acad. Sci. USA, 93: 4638-4643; referenced on page 11 and Figure 1 of the specification).

Lavie et al (J. Biol. Chem., Vol. 272, No. 3, pages 1682-1687, 1997) teach the correlation between decreased drug resistance and increased apoptosis following inhibition of glycosylceramide synthase in cancer cells in vitro (see abstract, introduction pages 1682-3, figure 3 on p. 1684, text on pp. 1686-7).

Ichikawa et al (Proc. Natl. Acad. Sci. USA, 93: 4638-4643, 1996) teach the DNA sequence and functional expression of human glucosylceramide synthase (figure 6, page 4642).

The primary references of Lavie and Ichikawa do not teach inhibition of glucosylceramide synthase expression using antisense.

Milner et al (Nature Biotech. 15: 537-541, 1997) teach assay devices and methods of designing and testing antisense for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach the in vitro inhibition of expression of a target gene using antisense (see col. 20, line 18 through col. 24, line 67; see also Tables 2 and 3 in col. 37-38).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense to inhibit the expression of glycosylceramide synthase in vitro, because Milner et al and McKay teach the ability to design and assess antisense in vitro for their ability to inhibit the expression of a target gene of known nucleotide sequence using routine screening assays that are well known in the art (see Milner at pages 539-540 and

McKay at col. 6-15). It would have been obvious to one of ordinary skill in the art to engineer antisense to glycosylceramide synthase since the sequence had been disclosed by Ichikawa et al. One of ordinary skill in the art would have been motivated to generate antisense to inhibit glycosylceramide synthase, since the motivation to generate cells which are deficient in glycosylceramide synthase had been disclosed by Ichikawa et al (last paragraph, page 4643), and the technology to generate antisense targeting a gene of known sequence was known to those of ordinary skill in the art, as had been taught by Milner et al and McKay. Furthermore, one of ordinary skill in the art would have been motivated to inhibit the synthesis of glucosylceramide in drug resistant cells because it had been taught in the prior art by Lavie et al that a correlation existed between decreased drug resistance and increased apoptosis in vitro with an inhibition of glucosylceramide synthase. One of ordinary skill in the art would have expected that the inhibition of the expression of glucosylceramide synthase using antisense in vitro leads to a decrease in glucosylceramide synthase activity and a concomitant decrease in drug resistance and increase in apoptosis in vitro.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 8-17-04 have been fully considered but they are not persuasive. Applicants argue that the combined references of Ichikawa et al, Lavie et al and Milner do not render the instantly claimed invention obvious because they fail to teach or fairly suggest introducing antisense to glucosylceramide synthase into a cell, whereby drug resistance is reversed in that cell. Contrary to Applicants' assertions, the combined teachings of Ichikawa et al, Lavie et al, Milner (and McKay) render the in vitro

reversal of drug resistance comprising administration of antisense to glucosylceramide synthase obvious. Lavie teaches a direct correlation between inhibition of glucosylceramide synthase activity and a decrease in drug resistance and increased apoptosis in cancer cells in vitro. Furthermore, the methods involved in designing and testing antisense for inhibiting a target gene in vitro for a target gene of known sequence was a matter of routine experimentation at the time the invention was made. Ichikawa taught the nucleic acid sequence of the target glucosylceramide synthase gene. Therefore, using routine experimentation, one would have reasonably expected that the inhibition of glucosylceramide synthase expression, leading the inhibition of glucosylceramide synthase activity, would also provide for decreased drug resistance and increased apoptosis, in a manner similar to the previous findings of Lavie et al. Therefore, the instant invention is rejected for being obvious to one of ordinary skill.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.**

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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